

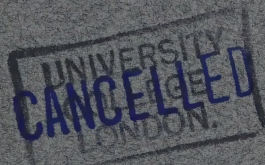
Reprinted from the American Journal of Physiology.

VOL. XXVIII. — APRIL 1, 1911. — No. 1.

EMOTIONAL STIMULATION OF ADRENAL SECRETION.

By W. B. CANNON AND D. DE LA PAZ.

[FROM THE LABORATORY OF PHYSIOLOGY IN THE HARVARD MEDICAL SCHOOL.]



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EMOTIONAL STIMULATION OF ADRENAL SECRETION.

BY W. B. CANNON AND D. DE LA PAZ.

[*From the Laboratory of Physiology in the Harvard Medical School.*]

IN 1891 Jacobi described nerves branching from the splanchnics and supplying the adrenal glands.¹ Six years later Biedl found that these nerves conveyed vaso-dilator impulses to the glands, and suggested that they probably conveyed also secretory impulses.² Evidence for this suggestion was presented the following year by Dreyer, who demonstrated that electrical stimulation of the splanchnics below the diaphragm produced in the adrenal blood an increased amount of substance raising arterial blood pressure and that this result was independent of accompanying vascular changes in the glands.³ The work of Dreyer has been confirmed by Tscheboksaroff⁴ and by Asher.⁵ The conclusion is justified, therefore, that adrenal secretion is under control of the thoracico-lumbar autonomic (sympathetic) system.

The phenomena of a major emotional exhibition in an animal indicate the dominance of sympathetic impulses. When, for example, a cat becomes frightened, the pupils dilate, the stomach and intestines are inhibited, the heart beats rapidly, the hairs of the back and tail stand erect — all signs of nervous discharges along sympathetic paths. Do not the adrenal glands share in this widespread subjugation of the viscera to sympathetic control?

In order to test this suggestion the natural enmity between two laboratory animals, dog and cat, was utilized. The cat, fastened to a comfortable holder, was placed near a barking dog. Some cats

¹ JACOBI: *Archiv für experimentelle Pathologie und Pharmakologie*, 1891, xxix, p. 185.

² BIEDL: *Archiv für die gesammte Physiologie*, 1897, lxvii, pp. 456, 481.

³ DREYER: *This journal*, 1898-1899, ii, p. 219.

⁴ TSCHEBOKSAROFF: *Archiv für die gesammte Physiologie*, 1910, cxxxvii, p. 103.

⁵ ASHER: *Zentralblatt für Physiologie*, 1910, xxiv, p. 927.

showed almost no signs of fear; others, with scarcely a movement of defence, made the typical picture of fright. In favorable cases the excitement was continued for five or ten minutes, and, in a few instances, longer. Samples of blood were taken within a few minutes before and after the period.

In the first experiments the blood was obtained by cardiac puncture. An attempt was made to test for the presence of adrenal secretion by the frog-eye method suggested by Meltzer⁶ and Ehrmann.⁷ The changes in size of the pupil, which were recorded by means of a camera lucida, did not give sufficiently striking results to permit drawing conclusions. Strips of beef artery, employed by Meyer,⁸ though highly sensitive, did not seem serviceable because of Schlayer's discovery that the method is less efficient when used with foreign blood.⁹ Structures natural to the blood to be tested were the uterus and strips of longitudinal muscle from the cat's intestine. Magnus showed, in 1905,¹⁰ that longitudinal intestinal muscle, contracting rhythmically, is characteristically inhibited by suprarenin, 1:20,000,000. Though this reaction has not hitherto been utilized as a biological signal for adrenal secretion, it possesses noteworthy advantages over the other methods. The strip is found in all animals, and not in only half of them, as is the uterus; it is ready for the test within a few minutes, instead of the several hours said to be required for the best use of the uterus method;¹¹ it need not be stretched in order to be ready to contract, as with the arterial strip; and it responds by relaxing. The last characteristic is especially important, since other substances in blood than adrenal secretion, as, for example, carbon dioxide, will cause smooth muscle to contract, whereas known substances evoking relaxation of smooth muscle are few and unusual in blood.¹²

⁶ MELTZER and C. M. AUER: This journal, 1904, xi, p. 449.

⁷ EHRMANN: Archiv für experimentelle Pathologie und Pharmakologie, 1905, liii, p. 97.

⁸ MEYER: Zeitschrift für Biologie, 1906, xlviii, p. 352.

⁹ SCHLAYER: Deutsche medizinische Wochenschrift, 1907, xxxiii, p. 1898.

¹⁰ MAGNUS: Archiv für die gesammte Physiologie, 1905, cviii, p. 48.

¹¹ FRAENKEL: Archiv für experimentelle Pathologie und Pharmakologie, 1909, lx, p. 399.

¹² GRÜTZNER: Ergebnisse der Physiologie, 1904, iii², p. 66; MAGNUS: *Loc. cit.*, p. 69.

The strip of longitudinal intestinal muscle, attached to a writing lever, was suspended between *serres fines* in a cylindrical chamber, 8 mm. in diameter and 5 cm. deep, through which oxygen passed. When not exposed to blood, the strip was immersed in Ringer's solution at body temperature. The chamber, the stock of Ringer's solution, and the blood samples were all surrounded by a large volume of water kept at approximately 37° C.

Although blood obtained by cardiac puncture gave in some cases characteristic results by this method, blood from the inferior vena cava was so much more regular and differential in its effects that it alone was finally used. To obtain blood from the inferior cava above the opening of the adrenal vessels, the skin over the femoral in the groin was made anæsthetic with ethyl chloride; the vein was bared, cleaned, tied, and opened; and a small flexible catheter (2.4 mm. diameter), coated with vaseline inside and out, was introduced through the iliac into the cava to near the level of the sternal notch. A ligature around the catheter at the point where it disappeared into the vessel permitted later reintroduction to the same extent. Since there was no sign of sensation when the catheter was slipped into the vein, it was possible to obtain "quiet blood," with only local anæsthesia. As soon as the blood (3 or 4 c.c.) was drawn, the catheter was removed and the vein tied. The blood was immediately defibrinated. After the animal had been frightened, the procedure was repeated, and thus the "excited blood" was secured. The two samples of blood, both treated in the same manner, and both kept at the same temperature as the contracting strip, were now tested.

The first effect of adding blood, whether quiet or excited, to the muscle strip was to send it into a strong contraction which might persist, sometimes with slight oscillations, for a minute or two (see Figs. 2 and 3). This contraction was not due to carbon dioxide, for removal of the blood gases and later restoration of oxygen did not alter the effect. Blood serum from centrifugated clot, and blood kept fluid by hirudin, produced equally the initial shortening.

After the initial shortening the strip, if in quiet blood, soon began to contract rhythmically and at the same time to lengthen more with each relaxation, until a fairly even base line appeared in the written record. At this stage the addition of fresh quiet blood usually had no effect, even though the strip were washed once with Ringer's

solution before the second portion of the blood was added. In comparing the effects of quiet and excited blood on the contracting strip, the two samples were each added to the strip immediately after removing the Ringer's solution, or they were applied to the strip alternately, and the differences in effect then noted.

That blood from the adrenal veins causes the relaxation of intestinal muscle characteristic of adrenal extract is shown in Fig. 1. The strip was originally beating in blood which contained no demonstrable amount of adrenal secretion; that blood was replaced by blood from the adrenal veins, obtained after quick etherization. Relaxation occurred almost immediately. Then the beats were renewed in the former blood, and thereupon the strip was immersed in blood from the left renal vein, obtained from the same animal and under the same conditions with the adrenal blood. No relaxation occurred. This and other similar tests proved the reliability of the method.

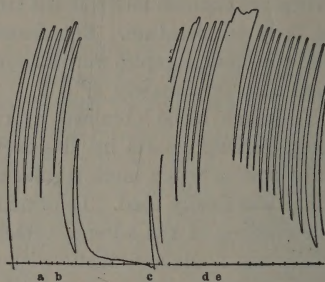


FIGURE 1. — Two fifths the original size. Intestinal strip beating in inactive blood which was removed at *a*. Blood from adrenal veins substituted at *b*, and removed at *c*. Contractions restored in inactive blood, removed at *d*; then blood from renal vein (same animal) added at *e*. In this and in the other tracings time is recorded in half minutes.

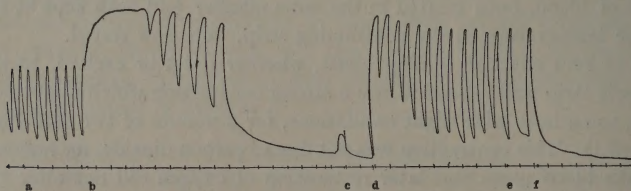


FIGURE 2. — About two fifths the original size. Alternate application of excited blood (at *b* and *f*) and quiet blood (at *d*), from the same animal, to an intestinal strip initially beating in Ringer's solution. See text for further description.

In no instance did blood from the quiet normal animal produce relaxation. On the other hand, blood from the animal after the emotional disturbance showed more or less promptly the typical relaxation. In Fig. 2 is presented the record of a strip which at first was

beating regularly in Ringer's solution. At *a* the Ringer's solution was removed and at *b* excited blood was added; after a preliminary short-

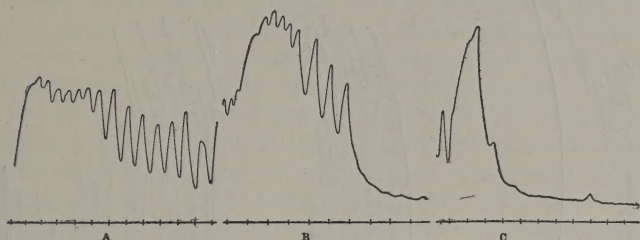


FIGURE 3. — About two thirds the original size. The effect of prolongation of excitement. *A*, the record in quiet serum; *B*, in defibrinated blood after eleven minutes of excitement, and *C*, in serum after fifteen minutes of excitement.

ening the strip lengthened gradually into an inhibition. At *c* the excited blood was removed, and at *d* quiet blood was added in its place. The strip at once began fairly regular rhythmic beats. At *e* the quiet blood was removed, and at *f* the excited blood again applied. The strip lengthened almost immediately into an inhibited state. In this instance the animal was excited about fifteen minutes.

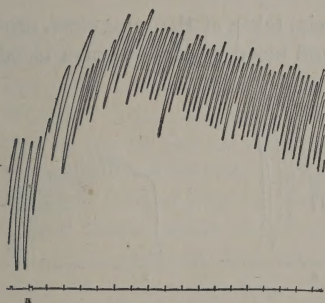


FIGURE 4. — One third the original size. The failure of blood to produce inhibition when excitement has occurred after removal of the adrenal glands. At *a*, blood added from inferior cava of excited animal previously deprived of adrenal glands. The strip later proved sensitive to adrenalin in blood in the ratio 1 : 1,000,000.

The increase of effect with prolongation of the emotional period is shown in Fig. 3. *A* is the record in quiet serum; *B*, the record in defibrinated blood after eleven minutes of excitement; and *C*, the record in serum after fifteen minutes of excitement. In other instances the effect was manifested merely by a lowering of the tonus of the strip and a notable slowing of the beats, without, however, a total cessation.

The view that the effects of excited blood are due to an increased

content of adrenal secretion is justified for several reasons. (1) The effect has been obtained in blood from the inferior vena cava near the

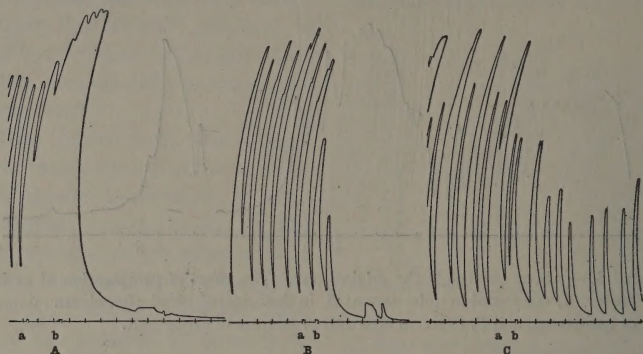


FIGURE 5.— About one half the original size. Effect of adding adrenalin 1 : 1,000,000 (A), 1 : 2,000,000 (B), and 1 : 3,000,000 (C), to formerly inactive blood. In each case *a* marks the moment when the quiet blood was removed, and *b*, the time when the blood with adrenalin was added.

liver, when blood from the femoral vein, taken at the same time, produced no inhibition. Since the femoral blood typifies the cava blood below the kidneys, the conclusion is warranted that the effect is not produced below the entrance of the kidney veins. That blood from the kidney veins does not cause the relaxation is shown in Fig. 1. (2) If the blood vessels of the adrenal glands are first carefully tied and the glands then removed, excitement four or five hours later does not alter the blood so that the typical effect occurs (see Fig. 4), although the animal shows all the characteristic indications of sympathetic stimulation. (3) Varying amounts of adrenalin added to blood which has not produced relaxation of the strip, evoke all the degrees of relaxation that have been observed in excited blood; Fig. 5 shows the

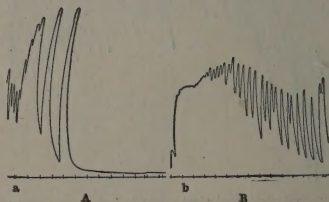


FIGURE 6.— One third the original size. The effect of bubbling oxygen through active blood. A, relaxation after active blood applied at *a*; B, failure of relaxation when the same blood, oxygenated three hours, was applied to a fresh strip at *b*.

effect of adding adrenalin, 1:1,000,000 (A), 1:2,000,000 (B), and 1:3,000,000 (C), to previously inactive blood. (4) Excited blood which produces inhibition loses that power on standing in the cold for twenty-four hours or on being kept warm and agitated with bubbling oxygen for only two or three hours. This last effect is illustrated in Fig. 6; the power to inhibit possessed when record A was written was lost in three hours in the presence of bubbling oxygen. Emden and v. Fürth have reported that 0.1 gm. of suprarenin chloride disappears almost completely in two hours if added to 200 c.c. of defibrinated beef blood, and the mixture constantly aerated at body temperature.¹³ All these considerations, taken with the evidence that sympathetic impulses increase the secretion of the adrenal glands, and that during such emotional excitement as was employed in these experiments, signs of sympathetic discharges were observable from the eye of the animal to the tip of its tail, prove that the characteristic effect of adrenal extract on the intestinal strips was due to secretion of the adrenal glands.

After excitement lasting ten minutes or more the effect was demonstrable not only in heart blood but also in blood from the femoral vein. As is well known, adrenal secretion itself is capable of working the effects evoked by sympathetic stimulation. Elliott reported that injected adrenalin discharges the adrenal glands so that the medullary cells stain less deeply with chromate salts, and yield no active extract.¹⁴ It is conceivable, therefore, that some of the adrenal secretion set free by nervous stimulation returns to the glands in the blood stream, and, within limits, stimulates them to further activity. Thus the more marked effect as time passes (see Fig. 3) may be due not only to further excitement, but in part to an autogenous continuance of adrenal secretion. Thus also the persistence of the emotional state after the exciting object has disappeared can be explained. Indeed it was the lasting effect of excitement on digestive processes which suggested this investigation.

¹³ EMBDEN and v. FÜRTH: *HOFMEISTER'S Beiträge zur chemischen Physiologie und Pathologie*, 1904, iv, p. 423.

¹⁴ ELLIOTT: *Journal of physiology*, 1905, xxxii, p. 427.



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